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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Bechtold-Peters *et al.*	Examiner:	Carlos A Azpuru
Serial No.:	09/975,418	Group Art Unit:	1500
Filed:	October 11, 2001	Docket:	1/1149

For: INHALABLE POWDER CONTAINING TIOTROPIUM

Assistant Commissioner for Patents
Washington DC 20231

DECLARATION OF KAROLINE BECHTOLD-PETERS UNDER 37 C.F.R. § 1.132

Sir:

I, Karoline Bechtold-Peters, declare that:

1. I have studied Pharmacy at the University of Munich, Germany from 1984 to 1989 (Degree: Pharmacist, "Approbierte Apothekerin").

2. I did my doctoral thesis in Munich at the Ludwig-Maximilians University, Germany from 1990 to 1994 and received a Ph.D. (Dr. rer. nat.) from the University of Munich, Germany in 1994.

3. Since 1994, I have been employed by Boehringer Ingelheim, presently in the Department of Process Sciences /Business Unit Biopharmaceuticals of Boehringer Ingelheim Pharma GmbH & Co. KG in Biberach, Germany.

4. I am familiar with the above-identified patent application (hereinafter "the Bechtold-Peters *et al.* application").

5. I am familiar with the U.S.P.T.O. Office Action dated June 29, 2004, and the prior art references cited therein: Arnold *et al.* (U.S. Patent No. 5,478,578; hereinafter "Arnold"), Ahmed *et al.* (U.S. Patent No. 6,235,725; hereinafter "Ahmed"), and Horhota *et al.* (U.S. Patent No. 6,228,394, hereinafter "Horhota").

6. The objective of the Bechtold-Peters *et al.* application is to ensure that tiotropium containing inhalable powder batches deliver the active ingredient in reproducibly more or less identical doses without a high variability from batch to batch. Under my responsibility and control, the influence of the amount of fine lactose in the powder mixture on the variability of the aerodynamic particle size of tiotropium containing capsules was determined according to the experimental procedure described in ANNEX 1. The variability of the aerodynamic particle size of tiotropium containing capsules is expressed by the RSD (= **r**elative **s**tandard **d**eviation) and range (= max – min) values of the fine particle fraction of different batches.

7. The experiment according to ANNEX 1 demonstrate that the batch to batch variability of the inhalable fraction is in comparison to powder mixtures containing no lactose 5 µm much lower when 5 % of lactose 5µm is added. The experiment according to ANNEX 1 further demonstrate that the batch to batch variability of the inhalable fraction is in comparison to powder mixtures containing no lactose 5 µm even lower, when 10 % of lactose 5µm is added. However, the experiment according to ANNEX 1 revealed in addition that the batch to batch variability of the inhalable fraction of powder mixtures containing 10% lactose 5 µm is higher than the batch to batch variability of powder mixtures containing 5 % of lactose 5µm.

8. The graphic illustration of the results obtained is depicted in ANNEX 2.

9. I hereby declare that the experimental results obtained for the tiotropium containing powder mixtures according to the Bechtold-Peters *et al.* application show that these powder mixtures allow the inhalable proportion of active substance tiotropium to be administered with the lowest possible variability. Furthermore, I conclude that this superiority of the Bechtold-Peters *et al.* powder mixtures was neither taught, suggested, nor deducible by the cited prior art. Moreover, I conclude that these findings would have been both surprising and unexpected to one of ordinary skill in the art at the time the invention was made.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and

further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 12.08.2004 Signature: Karoline Bechtold-Peters

(Karoline Bechtold-Peters)

ANNEX 1

Influence of the amount of lactose 5 µm in the powder mixture on the variability of the aerodynamic particle size of tiotropium capsules

Introduction:
For the investigation of the influence of the amount of lactose 5 µm in the powder mixture on the variability of the aerodynamic particle size of tiotropium capsules trials were performed with lactose 200 M as carrier with 0%, 5% and 10% admixture of lactose 5 µm.

Methods: Manufacturing
For the trials with 5% and 10% admixture of lactose 5 µm the micronized lactose was diluted with lactose 200 M in two stages using a sieve (Frewitt sieve-granulator with 315 µm metal screen) and a mixer (Turbula mixer; 900 revolutions).
Micronized tioptropium was diluted with lactose 200 M or the lactose premix in four stages using a sieve and a mixer.

The powder mixtures were filled into PEG-gelatine capsules using an automatic capsule filling machine (MG2 Futura).

The water content of the capsules was adjusted to 10% by conditioning at room temperature using air with reduced relative humidity (below 20% rh) and further with dry nitrogen.

Methods: Testing
The aerodynamic particle size of the capsules was determined by a Anderson Cascade Impactor and analysed using a HPLC method (High Pressure Liquid Chromatography).
taking samples from 10 different locations of the.

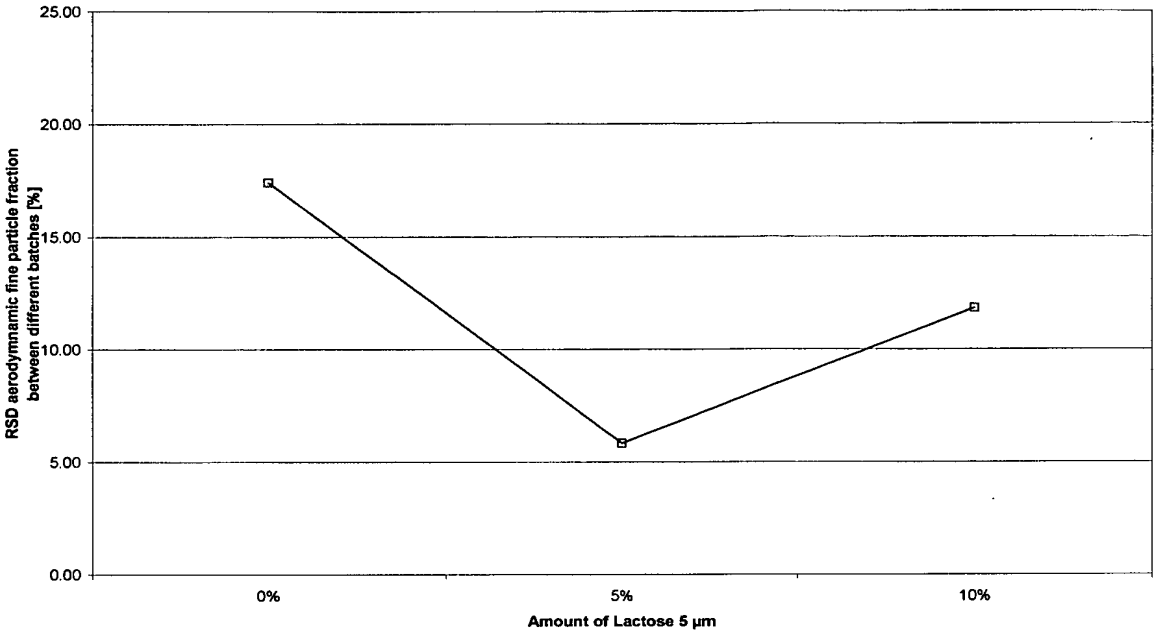
Assessment
To demonstrate the influence of the amount of lactose 5 µm in the powder mixture on the variability of the aerodynamic particle size of tiotropium capsules the following parameters were chosen:

- the RSD (= relative standard deviation) values of the fine particle fraction values of 6 different batches for each of the lactose 5 µm concentration levels 0% / 5% 10%;
  Unit: % of the respective mean value from the 6 batches with the same composition
- the range (= max – min) values of the fine particle fraction values of 6 different batches for each of the lactose 5 µm concentration levels 0% / 5% 10%;
  Unit: %-points between the minimum and the maximum of the 6 batches with the same composition

OIPE JC36
AUG 20 2004
PATENT & TRADEMARK OFFICE

ANNEX 2

Graph: Influence of the amount of Lactose 5µm on the inter-batch variation of the aerodynamic fine particle fraction: RSD values between different batches



Graph: Influence of the amount of Lactose 5µm on the inter-batch variation of the aerodynamic fine particle fraction: Range values between different batches